Editorials

A Single Inhaler for Asthma?

Despite the availability of highly effective therapies, many patients with asthma continue to suffer symptoms and exacerbations, with considerable disruption to their daily life (1). This may reflect underdiagnosis and inappropriate therapy, as well as poor adherence to regular prophylactic therapy. Inhaled corticosteroids are the mainstay of asthma therapy, but there is now compelling evidence that addition of a long-acting inhaled β_2-agonist (LABA: salmeterol or formoterol) gives better control in terms of reduced symptoms, improved lung function, and reduced exacerbations in patients with mild, moderate, and persistent asthma (2–4). This has led to the development of fixed combination inhalers (salmeterol/fluticasone, formoterol/budesonide), which are now increasingly used in asthma management (5, 6).

Combination inhalers are more convenient to use, control asthma at lower doses of corticosteroids, ensure that the corticosteroid is not discontinued when the bronchodilator is used, and are cost effective. There is a convincing scientific rationale for giving an LABA and corticosteroid together, as they have complementary actions on the complex pathophysiology of asthma and may enhance each other's effects at a molecular level (7). It is normal practice to administer these combination inhalers twice daily at a dose that is related to the severity of asthma and to use a short-acting β_2-agonist (SABA), such as albuterol, as required to relieve any breakthrough symptoms. Frequent use of the SABA indicates either poor compliance or the need for a higher maintenance dose of the combination inhaler. A recently published large study (over 3,000 patients) attempted to achieve better, and if possible total, control of asthma by progressively increasing the dose of the controller inhaler (8). Control was more easily and rapidly achieved with the salmeterol/fluticasone combination inhaler than fluticasone alone and at a lower total dose of inhaled corticosteroid. However, some patients required rather high doses of the combination inhaler to achieve satisfactory control of their asthma.

This issue of the *Journal* (pp. 129–136) presents a new study that takes this approach a step further (9). It had previously been shown that formoterol could be used as a reliever medication in asthma, as it has a rapid onset of action with a long bronchodilator effect, yet systemic side effects are of a similar duration to an SABA (10). In the new double-blind controlled parallel group study (involving over 2,500 patients) formoterol/budesonide combination inhaler was used as maintenance therapy twice daily, but additional puffs were used as needed for symptom relief (9). This was compared with the same maintenance dose and to a fourfold greater dose of budesonide alone, both with terbutaline as needed. The remarkable, and somewhat unexpected, finding was that the treatment with combination inhaler for both maintenance and relief markedly reduced the number of severe exacerbations (the primary outcome measure) over the 1-year treatment period compared with the other treatments, but also reduced the need for oral corticosteroids, improved symptom control, and lung function compared with the other treatment regimens. A concern about this approach is that some patients might end up using the combination inhaler frequently and therefore receive an unacceptably high dose of inhaled corticosteroid. However, this was not the case, as the mean number of additional doses of combination inhaler was only one dose per day and very few patients used high doses. Combination inhalers have generally been less effective in children with asthma (11), as LABA do not appear to have such a large add-on effect. In this study, children aged 4–11 years (12% of study population) were also included, but there is no information provided on how they responded to the different treatment strategies compared with adults.

How can these surprisingly good results be explained mechanistically? Asthma is characterized by variable symptoms with day-to-day variability. One approach to deal with such variability is by giving a high dose of combination inhaler to prevent the emergence of symptoms, as adopted by the salmeterol/fluticasone study (8). An alternative approach is to increase the treatment at the time asthma worsens. We know from the careful analysis of asthma exacerbations in a large controlled trial that they evolve slowly over a few days (12). This provides the opportunity to intervene before the exacerbation develops fully. It is now clear that doubling the maintenance dose of inhaled corticosteroid is insufficient to prevent an exacerbation (13), whereas a fourfold increase is effective (2), and confirmed by the present study. It is likely that the combination inhaler not only provided an effective bronchodilator to relieve symptoms, but also a steroid at a time when it is needed. It is now emerging that inhaled corticosteroids work much more rapidly than previously recognized, with significant antiinflammatory and bronchoprotective effects detectable after a few hours (14, 15). The reason why the additional rescue treatment with the combination inhaler on top of the maintenance dose is so effective is presumably related to timing and its effect of "nipping in the bud" the evolution of an exacerbation. It is likely that the corticosteroid component is most important in this respect, although this needs to be demonstrated in a controlled trial using formoterol, rather than terbutaline, as the rescue therapy. It may, however, be the combination of the two drugs that is important, with some critical interaction between the LABA and the corticosteroid which enhances the effectiveness of this approach. Further research is now needed to understand the molecular mechanism involved and whether this approach more effectively controls airway inflammation.

The study by O'Byrne and colleagues may lead to changes in the paradigm of asthma management, where a single inhaler is used for both maintenance and rescue (9). This simplifies asthma therapy for the patients (and the doctor) and is likely to improve compliance. It also follows more closely what patients do in the real world, where they tend take more medication in response to increased symptoms. It is also likely that this treatment strategy will be more cost effective as better control of asthma reduces the costs of treating exacerbations and hospital admissions. We now need effectiveness studies in the real world to see whether this simplified approach is applicable to treating asthma patients in the community (16).

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Therapeutic Hypercapnia: Careful Science, Better Trials

Reducing tidal volumes in patients with injured lungs—a strategy associated with elevated carbon dioxide—improves patient survival (1, 2). Laboratory studies have documented benefits of hypercapnia, as well as some mechanisms of action (3–5). Moreover, buffering hypercapnic acidosis attenuates its benefit, and hypocapnia can be harmful (6). All of the above suggests that hypercapnia might soon evolve into a testable clinical therapy (7).

In the current issue of the *Journal* (pp. 147–157), a paper from Lang and coworkers injects a dose of disquiet into this evolving carbon dioxide story (8). The authors have investigated an animal model of sepsis and found that their particular strategy of permissive hypercapnia increased—not decreased—lung inflammation (8). This article follows an earlier report of adverse effects of hypercapnia from the same group (9), multiple studies of its free radical biochemistry (10), and extensive experience at the bedside—particularly with pulmonary or intracranial hypertension.

So there are two sides to the hypercapnia story and a spectrum of interpretations. The current study is superficially at odds with several previous studies (5, 11–13), including some from our laboratory. The worst possible approach would be to ignore or condemn the new data because they do not fit with one's prior ideas. This would be anti-science. The appropriate approach is to review all the information carefully to understand it fully.

How then, do we learn from the current data? I see three questions and three lessons. First, are the findings of the current study attributable to hypercapnia, or to the means of achieving it? Lang and colleagues allocated animals to a strategy of "permissive hypercapnia" by lowering the respiratory rate, not the tidal volume (8). Of course, achieving "permissive hypercapnia" by reducing respiratory rate is unusual at the bedside. In fact, clinicians usually reduce tidal volume, and to compensate, increase the respiratory rate. This may be important, because low values of tidal volume, positive end-expiratory pressure, and respiratory rate may cause atelectasis. Indeed, it has been suggested that benefits associated with one low tidal volume strategy may actually be due to intrinsic positive end-expiratory pressure resulting from the increased respiratory rate (14). As well, the authors remind us that in contrast to adding inspired carbon dioxide, hypoventilation may result in uneven distribution of carbon dioxide throughout the lung (15). Indeed, "therapeutic hypercapnia," through raising the arterial carbon dioxide by increasing inspired concentration, is not frequently practiced in the clinical setting but has proved effective in the laboratory (5). Finally, the authors point out that the use of 100% inspired oxygen (8), a level avoided by most clinicians, might have exacerbated inflammatory events (16). Therefore, in answer to the first question, all hypercapnia may not be equal, and the differences may in part be due to other aspects of the ventilatory management.

Second, what do we learn about the complexity of hypercapnia? The current study expands our horizons regarding the pathogenic mechanisms associated with elevated levels of carbon dioxide which can alter the formation of peroxynitrite, and result in either "relatively protective" or "relatively injurious" intermediates. The authors discuss the recent study by Laffey and coworkers that demonstrated protection against endotoxin-induced lung injury with added carbon dioxide (11). Whereas that study suggested that the nitrotyrosine formation might represent a reservoir that could "mop up" the more toxic nitrate/nitrite intermediates in the lung (11), the current study demonstrated that inhaled nitric oxide decreased tissue injury (8), but without altering the formation of nitrotyrosine. Thus, in answer to the second question, inhaled nitric oxide may lessen lung injury associated with endotoxin and hypercapnia, and illustrates the lesson that nitrotyrosine formation might be more a marker of injury than a pathogen.

Third, what are the implications for rapid implementation at the bedside? There is an intense personal and professional desire within all of us to get results for patients—and quickly. This was